Research Article

Use of urinary PO_2 for early detection of renal dysfunction in cardiac surgical patients

Ramesh Patel[1], Harshil Joshi[1], Hasmukh Patel[1], Jignesh Kothari[2], Himani Pandya[3], Atul Solanki[4]

[1]Department of Cardiac Anaesthesia, U N Mehta Institute of Cardiology and Research Center (Affiliated to B J Medical College), Ahmedabad, Gujarat, India.
[2]Department of Cardiovascular and Thoracic Surgery, U N Mehta Institute of Cardiology and Research Center (Affiliated to B J Medical College), Ahmedabad, Gujarat, India.
[3]Department of Research, U N Mehta Institute of Cardiology and Research Center (Affiliated to B. J. Medical College), Ahmedabad, Gujarat, India.
[4]Department of Perfusion, U N Mehta Institute of Cardiology and Research Center (Affiliated to B J Medical College), Ahmedabad, Gujarat, India.
Correspondence to: Ramesh Patel, E-mail: dr.ramesh33@gmail.com

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Abstract

Background: Medullary hypoxia is a critical initiating event in the development of multiple forms of acute kidney injury (AKI), and the urinary PO_2 provides an index of medullary oxygenation. This biomarker has the potential to aid in the management of patients at risk of AKI and, so, to possibly prevent development of AKI.

Objective: To evaluate the effect of cardiopulmonary bypass (CPB) on urine oxygen tension (PO_2) and determine whether perioperative PO_2 can predict postoperative renal dysfunction in patients undergoing cardiac surgery.

Materials and Methods: This prospective, observational study has enrolled a total of 63 patients who were undergoing on-pump cardiac surgery. On the basis of the AKI guideline, the patients were distributed into two groups. Group A patients did not develop AKI (n = 45), and the remaining patients developed AKI: group B (n = 12). Preoperative renal data and intraoperative and postoperative data were collected.

Result: Urine PO_2 data were recorded for 63 patients from blood gas analyzer. Prebypass and postbypass urine PO_2 was similar up to 24-h postoperative in all patients. Even in patients who develop AKI, we did not find any difference in urine PO_2 prebypass and postbypass.

Conclusion: These results suggest the possibility of PO_2 detecting an early stage of renal dysfunction in cardiac surgery although further studies will be required to substantiate it.

KEY WORDS: Urine oxygen tension, cardiopulmonary bypass, renal dysfunction, acute kidney injury

Introduction

Cardiac surgery is associated with a significant risk for the development of acute kidney injury (AKI).[1] AKI is associated with a major increase in mortality, morbidity, and resource utilization both immediately after surgery and in the long term.[1,2] Despite significant advances in hemodynamic monitoring and surgical skill, AKI prevalence and mortality rate is not much improved. Baseline serum creatinine can help identify those patients at risk of hospital-acquired AKI.[3] Serum creatinine can also be used to follow the progression of AKI. But, increase in serum creatinine lag many hours behind the development of AKI. Multiple plasma and urinary biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), have shown some efficacy in an early prediction of AKI,[4] but such molecules are markers of renal injury. An absolute biomarker would yield details about the functional status of the kidney in individual patients so that conditions likely to stimulate occurrence of AKI can be avoided. Although

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the pathophysiology of acute renal injury remains obscure, the precarious balance of oxygen supply and demand in the renal medulla (medullary hypoxia) has been implicated in the development of AKI.[5] Unfortunately, the development of kidney ischemia, so-called "renal angina," is painless and, to date, cannot be clinically monitored. The kidney is a highly perfused organ, and the medulla receives only 5% of total renal blood flow. In addition to poor oxygen delivery, high oxygen demand by the medullary tubular cells assures that "normal" medullary PO_2 is always significantly lower than renal artery or vein oxygen levels. Our hypothesis is based on the evidence that medullary hypoxia is a critical initiating event in the development of multiple forms of AKI and that urinary PO_2 provides an index of medullary oxygenation. This biomarker has the potential to aid in the management of patients at risk of AKI and, so, to possibly prevent development of AKI. To validate this hypothesis, we have measured perioperative urine PO_2 in patients undergoing on-pump cardiac surgery, which potentially exposes kidney to hypoxia, and examined how it related to postoperative variables of renal function.

Materials and Methods

Study Design

Elective patients undergoing on-pump cardiac surgery who fulfilled the study criteria were recruited following informed consent. Study was approved by our institutional ethics committee. Study was done in the period from May 2015 to June 2015 at UN Mehta Institute of Cardiology and Research Center, Ahmedabad, India. This was a prospective, observational study designed to know whether PO_2 of urine can be taken as an early marker of AKI in patients undergoing cardiac surgery or not. This prospective study enrolled 63 patients who underwent on-pump cardiac surgery. All surgeries were done by surgeons trained in cardiac surgery with more than 10 years of experience.

Anesthesia

A standardized protocol was followed for induction and maintenance of anesthesia. Anesthetic administration of anxiolytics, narcotics, and muscle relaxants was similar in all patients. Each patient revealed continuous perioperative monitoring of central venous, systemic arterial pressures, SpO_2, ECG, and nasopharyngeal temperature.

CPB Management

A standard adult extracorporeal tubing set was used incorporating a 40-μm arterial line filter in conjunction with a Trillium® Affinity NT® Hollow Fiber Oxygenator (Medtronic, Ltd., USA). The circuit was primed with 1500 mL of Ringer lactate, 50 mL 20% mannitol, 50 mL sodium bicarbonate, and 7000 IU of sodium heparin. An S3 roller pump (Stöckert Instrumente GmbH, Munich, Germany) controlled nonpulsatile flow that was maintained at or above 2.5L/min/m^2. The procedure was conducted under moderate hypothermia (32.8°C) with myocardial protection provided by intermittent antegrade or retrograde cold blood cardioplegia (48°C). The cardioplegic mixture consisted of St. Thomas solution. Diastolic cardiac arrest was induced with 20 L/kg of cardioplegic infusion supplemented at 20-min intervals by further doses. The mean perfusion pressure was titrated between 50 and 70 mm Hg with a combination of phenylephrine and sevoflurane. Alpha-stat management of acid–base status was used during cardiopulmonary bypass (CPB). Blood PO_2 was maintained between 200 and 300 mm Hg. Hematocrit was adjusted between 25% and 30%.

Methods for Measurement of Urinary PO_2

Consideration should be given to the best approach for measurement of the PO_2 of bladder urine in humans. There are various instruments available for measurement of PO_2 of bladder urine such as polarographic electrodes, fiberoptic probes, magnetic resonance imaging, and standard blood gas analyzer. Owing to technical limitation and availability of instruments, we have used blood gas analyzer (Cobas b 221) for the measurement of bladder urine PO_2. Urine sample was taken with a needle directly from Foley's catheter in a 2-cc new plain syringe. First, urine sample was taken 15 min before going for bypass, second sample was taken 15 min after coming from bypass, and third and fourth sample was taken 2 h and 24 h after completion of surgery.

Assessment of Renal Function

Blood samples were collected from each patient preoperatively and until postoperative day 3. Changes in renal function were assessed by measuring blood urea and serum creatinine (Cr). Urine output was also measured until day 3. Demographic variables and perioperative characteristics were also collected. Inotropic duration, ventilation duration, and intensive care unit (ICU) and hospital stays were also measured. Blood product requirement was also calculated.

Definition of RD/AKI

We have excluded patients with preoperative serum creatinine (Cr-Pre) values > 1.5 mg/dL, those on hemodialysis, those taking nephrotoxic drugs, and patients whose OPCAB converted to CPB. The analysis also excluded patients with CAG performed 72 h before the surgery [Table 1].

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age between 18 and 65 years	Preexisting renal disease
Elective surgery	Serum creatinine above 1.5 mg/dL
On-pump cardiac surgery	LV ejection fraction less than 35%
EF more than 35%	Surgery within 72 hours of CAG
	Uncontrolled hypertension
	Age older than 65 years
	Regular usage of nephrotoxic agents
	Emergency surgery

Table 2: Demographic data

Variables	Group A ≤0.3	Group B >0.3	*P*
Age (years)	48.26 ± 11.32	51.83 ± 11.91	0.269
Sex	M = 23, F = 22	M = 10, F = 8	
Height (cm)	158.70 ± 9.65	157.72 ± 10.75	0.726
Weight (kg)	52.44 ± 11.05	54.44 ± 12.17	0.531
BSA (m^2)	1.16 ± 0.64	1.29 ± 0.62	0.642

BSA, body surface area.

Table 3: Preoperative and intraoperative findings

Variables	Group A ≤0.3	Group B >0.3	*P*
Preop. urea (mg/dL)	26.94 ± 11.32	31.58 ± 10.60	0.149
Preop. creatinine (mg/dL)	0.76 ± 0.10	0.82 ± 0.09	0.057
CPB time (min)	109.53 ± 51.29	138.88 ± 61.47	0.572
AoX time (min)	85.31 ± 46.62	108.88 ± 53.65	0.880

CPB, cardiopulmonary bypass; AoX, aortic cross-clamp.

Table 4: Postoperative findings

Variables	Group A ≤0.3	Group B >0.3	*P*
First POD urea (mg/dL)	30.82 ± 10.29	41.31 ± 11.26	0.001
Second POD urea (mg/dL)	33.45 ±12.66	51.58 ± 17.73	<0.001
First POD creat (mg/dL)	0.84 ± 0.17	1.39 ± 0.42	<0.001
Second POD Creat (mg/dL)	0.80 ± 0.17	1.29 ± 0.55	<0.001
First POD U/O (mL/kg/h)	2031.17 ± 490.29	1932.16 ± 488.64	0.2695
Second POD U/O (mL/kg/h)	2046.55 ± 537.70	1888.23 ± 377.18	0.270
First POD creat. clear (mL/min)	79.91 ± 19.01	46.87 ± 14.84	<0.001
Second POD creat. clear (mL/min)	85.14 ± 22.06	55.56 ± 24.34	<0.001
Mechanical ventilation time (h)	5.68 ± 6.56	6.77 ± 3.78	0.512
Postop. ICU stay (days)	3.11 ± 2.94	3.77 ± 1.47	0.366

POD, postoperative day; U/O, urine output; ICU, intensive care unit.

Table 5: Urine PO_2 at different time points

Variables	Group A ≤0.3	Group B >0.3	*P*
At induction time urine PO_2	152.80 ± 148.05	126.13 ± 25.14	0.452
After shifting to ICU urine PO_2	135.01 ± 152.53	121.20 ± 19.76	0.704
2 h after shifting urine PO_2	120.69 ± 18.39	119.04 ± 11.85	0.726
24 h after shifting urine PO_2	122.43 ± 16.30	119.44 ± 18.96	0.535

ICU, intensive care unit.

We considered AKI when patients serum creatinine was raised ≥ 0.3 mg/dL within 48 h or increase in serum creatinine ≥ 1.5 times baseline, which is known or presumed to have occurred within prior 7 days or urine volume < 0.5 mL/kg/h for 6 h according to KDIGO, AKI practice guideline.

Statistical Analysis

Statistical analysis was carried out using SPSS software, version 20.0 (SPSS, Inc., USA). The χ^2-test and independent sample *t*-test were used to compare categorical and continuous variables, respectively. Data were presented as mean ± SD or proportion as appropriate. The "*p*" value less than 0.05 was considered to be significant.

Result

In this study, we have enrolled a total of 63 patients who were undergoing different on-pump cardiac surgery. All the postoperative data such as urea, creatinine, urine output, and

creatinine clearance were recorded. On the basis of the AKI guideline, patients were distributed into two groups. Group A patients included those who developed AKI (n = 12), and the remaining patients were in group B.

Baseline demographic and preoperative clinical characteristics age (group A 48.26 ± 11.32 years vs. group B 51.83 ± 11.91 years; p = 0.269), height (group A 158.7 ± 9.65 cm vs. group B 157.72 ± 10.75 cm; p = 0.726), and weight (group A 52.44 ± 11.05 kg vs. group B 54.44 ± 12.17 kg; p = 0.531) were statistically nonsignificant in both groups [Table 2]. Preoperative creatinine, urea, intraoperative CPB time, and cross-clamp time were also statistically nonsignificant between the two groups [Table 3].

Postoperative parameters such as creatinine, creatinine clearance, and urea were found statistically significant between the two groups, but urine output was found statistically nonsignificant between the two groups [Table 4].

Urine PO_2 data were recorded for 63 patients from blood gas analyzer. Prebypass and postbypass urine PO_2 was similar up to 24-h postoperative in all patients. Even in patients who developed AKI, we did not find any difference in urine PO_2 prebypass and postbypass [Table 5].

Discussion

We conducted a prospective, observational study to investigate whether urinary PO_2 can be taken as early marker for renal injury. In this prospective, observational study, we found that urinary PO_2 is not related to postoperative renal dysfunction.

Hypoxia in the renal medulla is a hallmark of AKI of diverse causative factors. Our hypothesis is based on the evidence that medullary hypoxia is a critical initiating event in the development of multiple forms of AKI. Medullary blood flow, per unit tissue, is much less than cortical blood flow.[6] The renal medulla is perfused by the vasa recta and forms a hairpin structure in medulla.[7] Countercurrent exchange of oxygen occurs from the descending to the ascending branches of loop of Henle. This will decrease oxygen supply to the deeper portions of medulla.[8] The outer medulla contains the thick ascending limbs of Henle's loop, which reabsorb much of the filtered sodium and, therefore, require a large amount of oxygen. Yet, this region has a comparatively less oxygen supply.[9] Consequently, in human, AKI tubular damage is most often seen in the distal segments of nephrons in the outer medulla (thick ascending limbs and collecting ducts).[10] Evidence that prevention of kidney ischemia and hypoxia should reduce the risk of AKI comes from studies of AKI after CPB surgery. Many of the risk factors for AKI after CPB surgery are associated with reduced renal perfusion (and, thus, oxygen delivery) and/or increased renal oxygen consumption. It has been argued that tissue hypoxia may initiate a vicious cycle in AKI, leading to progression of kidney disease and worsened tissue hypoxia.[6,11,12] We assume that urine in the collecting ducts would equilibrate with the tissue PO_2 of the inner medulla, as the collecting ducts exiting at the renal papilla run parallel, and in close association with, the vasa recta. Accordingly, the PO_2 of urine in the renal pelvis changes in response to changes in oxygenation of the renal medulla. Urinary PO_2 provides an index of medullary oxygenation. Because the delay between medullary hypoxia and measurement of urinary hypoxia should be only minutes, this biomarker has the potential to aid in the management of patients at risk of AKI and, so, to possibly prevent development of AKI. To assess the potential utility of urinary PO_2 as a marker of medullary oxygenation and as a biomarker for risk of AKI, we review the relevant literature as described further.

In a study of 60 patients admitted to coronary ICUs for acute myocardial infarction or unstable angina, Kitashiro et al.[13] noted that urinary catheter PO_2 was related to cardiac index and serum creatinine values and suggested that urinary oxygen levels can be used as a noninvasive indicator of renal function in patients with ischemic heart disease. In a study of 98 patients undergoing cardiac surgery, Kainuma et al.[14] noted that postoperative serum creatinine was significantly higher in patients whose urine PO_2 decreased after CPB.

But, we did not find any significant relation between urine PO_2 and postoperative incidence of AKI. It may be because there are some limitations of our study design. There are some issues in practical and theoretical fields, which need to be answered. First, it still remains unclear whether urine PO_2 actually reflects medullary oxygen in normal kidney or not. Second, oxygen exchange across the walls of the ureter and bladder will confound measurement of the PO_2 of bladder urine. Landes et al.[15] and Legrand et al.[16] found, in normal human subjects, that urinary PO_2 fell from 48 to 33 mm Hg along the ureter from the renal pelvis to the bladder. Nevertheless, the PO_2 of bladder urine also changes in response to stimuli that would be expected to alter renal medullary oxygenation. If confounding influences can be understood, urinary bladder PO_2 may provide prognostically useful information, including for prediction of AKI after CPB surgery. Third, polyethylene used in Foley catheter is permeable to oxygen.[17] Rennie et al.[17] also found that urine could consume oxygen. Finally, we have not used continuous urine PO_2 measurement tool.

Conclusion

Our theoretical knowledge suggest that urine PO_2 can be used as a strong indicator for prediction of AKI, but our practical results are not matching with the same. To substantiate urine PO_2 as a predictor of AKI, we need more advance measurement tool and more study with large sample size.

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